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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference PCT/P89103PWO | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/GB03/01623 | International filing date (day/month/year) 15.04.2003 | Priority date (day/month/year) 17.04.2002 |
| International Patent Classification (IPC) or both national classification and IPC C12N9/12 | | |
| Applicant THE UNIVERSITY OF NEWCASTLE et al. | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application | | |
| Date of submission of the demand 22.10.2003 | Date of completion of this report 18.12.2003 | |
| Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Armandola, E Telephone No. +49 89 2399-7493 | |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB03/01623

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-25 as originally filed

Claims, Numbers

1-26 as originally filed

Drawings, Sheets

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-43, filed with the letter of 12.6.03,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

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5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-26 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-26 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-26 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents

- D1: GREAGG M A ET AL: 'A read-ahead function in archaeal DNA polymerases detects mutagenic template-strand uracil.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 3 AUG 1999, vol. 96, no. 16, 3 August 1999 (1999-08-03), pages 9045-9050, XP002250142 ISSN: 0027-8424
- D2: EVANS S J ET AL: 'Improving dideoxynucleotide-triphosphate utilisation by the hyper-thermophilic DNA polymerase from the archaeon *Pyrococcus furiosus*.' NUCLEIC ACIDS RESEARCH. ENGLAND 1 MAR 2000, vol. 28, no. 5, 1 March 2000 (2000-03-01), pages 1059-1066, XP002164138 ISSN: 1362-4962
- D3: FOGG MARK J ET AL: 'Structural basis for uracil recognition by archaeal family B DNA polymerases.' NATURE STRUCTURAL BIOLOGY. UNITED STATES DEC 2002, vol. 9, no. 12, December 2002 (2002-12), pages 922-927, XP002250141 ISSN: 1072-8368

Document D3 was published after the priority date but before the filing date of the present application. It does, therefore, not constitute part of the state of the art in the meaning of Rule 64(1)(b) PCT. At the moment the validity of the priority claimed by the present application cannot be checked as the priority document is not yet available. However, if it later turns out that the priority of the present application has not been correctly claimed, D3 will become of relevance for the novelty and for the inventive step of the claimed subject-matter.

Novelty and Inventive step (Art. 33(2), Art. 33(3) PCT)

The subject-matter of claims 1-26 can be considered novel and inventive for the following reasons.

The *wild-type* nucleotide and amino acid sequences of the archaeal DNA polymerases mutated in the application were known as well as some of their crystal structures (see,

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for example, references cited in the description, page 17). However, no suggestion on how to improve these polymerases by decreasing their affinity for uracil can be found in the prior art. The problems linked to the mutagenic potential of uracil had been recognized in the prior art (see e.g. D1), but no solution had been proposed. The DNA polymerase of *P. furiosus* had been modified to improve its utilization of ddNTPs (see D2), but the residues mutated as well as the purpose of these mutations are different from those described in the application.

The applicant's attention is drawn to the fact that claims 1-4 contain no reference to the sequences of the polymerases and are, therefore . considered unclear (Art. 6 PCT).